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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,040	11/15/2000	Paul J. Carter	P0710P1D1	5212

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/714,040	CARTER, PAUL J.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 25 and 29 are pending.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/22/2004 has been entered.

3. Claim 25 has been amended and claim 28 has been cancelled in the paper filed 4/22/2004.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

Response to Arguments

6. The rejection of claim 25 under 35 U.S.C. 112, first paragraph, as containing subject matter which, was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of Applicant's arguments.

New Grounds of Rejections

Claim Objections

7. Claim 29 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Claim 29, which depends from base claim 25 recites that each Fab comprises the C-terminal amino acid sequence Cys-Ala-Ala, however, base claim 25 recites that the heavy chain is homogenous only for the C-terminal amino acid and not the C-terminal three amino acids. Thus, the C-terminal tripeptide recited in dependent claim 29 broadens the scope of base claim 25.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claim 25 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25 and 29 are indefinite for reciting "homogenous as to the heavy chain C-terminal amino acid residue" in claim 25. Dependent claim 29 recites wherein the C-terminal amino acid sequence is Cys-Ala-Ala. It is unclear whether the phrase

"homogenous as to the heavy chain C-terminal amino acid residue" means that only the C-terminal alanine is homogenous in the two heavy chains or are the heavy chains homogeneous in that they comprise the C-terminal tripeptide sequence Cys-Ala-Ala?

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by Rhind S. K. (WO 90/09196, 8/23/1990).

Claim 25 is interpreted as drawn to a composition comprising a monospecific $F(ab)_2$ wherein each F(ab) of the $F(ab)_2$ has only one hinge region cysteine and does not contain hinge region intrachain disulfide bonds, is free of contaminating arsenite and is homogenous as to the heavy chain C-terminal amino acid residue.

Rhind teaches a $F(ab)_2$ that is specific for one antigenic determinant (i.e., monospecific) and having only one hinge region cysteine in each heavy chain, which is used to form a non-disulphide interchain bridge (see entire document, particularly page 10, lines 1-3 and 21-30 and page 3, lines 12-19). $F(ab)_2$ having only one hinge region cysteine in each heavy chain would inherently be free of intrachain disulfide bonds, since intrachain disulfide bonds are formed between two SH groups in the same chain.

Rhind does not teach a $F(ab)_2$ comprising arsenite. Therefore, it is the Examiners position that the $F(ab)_2$ taught by Rhind is free of contaminating arsenite. Further, because an antibody molecule consists of two identical light chains and two identical heavy chains, the $F(ab)_2$ taught by Rhind inherently is homogenous as to the heavy chain C-terminal amino acid residue. Therefore, Rhind et al anticipate the claim.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 25 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhind S. K. (WO 90/09196, 8/23/1990) in view of Cunningham et al (Science, 244(4908):1081-1085, 6/2/1989).

Claim 25 has been described supra.

Claim 29 is interpreted as further limiting base claim 25 in reciting that each Fab of the $F(ab)_2$ comprises the heavy chain C-terminal amino acid sequence Cys-Ala-Ala.

Rhind has been described supra. Rhind also teaches alanine substitutions in the hinge region (see page 15, lines 3-7). Rhind does not specifically teach the C-terminal amino acid sequence Cys-Ala-Ala. This deficiency is made up for in the teachings of Cunningham et al.

Cunningham et al teach that alanine substitutions eliminate the side chain beyond the β carbon, yet do not alter the main-chain conformation (as can glycine or proline) nor does it impose extreme electrostatic or steric effects (see page 1081, left column). Cunningham et al also teaches that alanine is the most abundant amino acid and is found frequently in both buried and exposed positions and all variety of secondary structures (see page 1081, left column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a monospecific $F(ab)_2$ wherein each F(ab) of the $F(ab)_2$ has only one hinge region cysteine and does not contain hinge region intrachain disulfide bonds, is free of contaminating arsenite and is homogenous as to the heavy chain C-terminus, having the amino acid sequence Cys-Ala-Ala.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a monospecific $F(ab)_2$ wherein each F(ab) of the $F(ab)_2$ has only one hinge region cysteine and does not contain hinge region intrachain disulfide bonds, is free of contaminating arsenite and is homogenous as to the heavy chain C-terminus, having the amino acid sequence Cys-Ala-Ala in view

of Rhind and Cunningham et al because Rhind teaches a monospecific $F(ab)_2$ that has only one hinge region cysteine in each heavy chain, is inherently free of intrachain disulfide bonds and Rhind teaches alanine substitutions in the hinge region and Cunningham et al teach that alanine substitutions eliminate the side chain beyond the β carbon, yet do not alter the main-chain conformation (as can glycine or proline) nor does it impose extreme electrostatic or steric effects. Therefore, it would have been obvious to have produced a non-disulfide linked $F(ab)_2$ wherein each Fab heavy chain comprises the C-terminal sequence of Cys-Ala-Ala because the single cysteine in the sequence Cys-Ala-Ala allows the directed formation of inter-Fab non-disulfide bonds as taught by Rhind and the two alanines provide stability and protection to the non-disulfide interchain bridge without affecting the main chain conformation or imposing electrostatic or steric effects as taught by Cunningham et al. Thus, it would have been obvious to one skilled in the art to have produced a monospecific $F(ab)_2$ wherein each F(ab) of the $F(ab)_2$ has only one hinge region cysteine and does not contain hinge region intrachain disulfide bonds, is free of contaminating arsenite and is homogenous as to the heavy chain C-terminus, having the amino acid sequence Cys-Ala-Ala in view of Rhind and Cunningham et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

14. Claims 25 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glennie et al (The Journal of Immunology, 139(7):2367-2375, 1987, Ids reference

44) in view of Wahl et al (The Journal of Nuclear Medicine, 24(4):316-325, 1983) and Cunningham et al (Science, 244(4908):1081-1085, 6/2/1989).

The claims and their interpretation have been described supra.

Glennie et al teach a bispecific $F(ab)_2$ containing thioether linked Fab fragments and coupling can occur through a single hinge region cyteinyl sulfur (see Figure 8 and last line of the legend). Further, it is readily apparent to the skilled artisan from the teachings of Glennie et al that $F(ab)_2$ having more than one cysteine in the hinge region results in heterogeneity in $F(ab)_2$ preparations such as intra-hinge disulfide formation and contamination with intact parent antibody as well as a minor species of $F(ab)_3$ with $F(ab)_2$ being the major species produced at 50-70% of the final product (see page 2369, right column and page 2373, right column and Figure 2). Glennie et al teaches that disulfide-linked $F(ab)_2$ are susceptible to attack by trace amounts of thiol, however, the thioether-linked $F(ab)_2$ ensures that they remain intact (see page 2374, right column). Glennie et al do not teach a $F(ab)_2$ comprising arsenite. Therefore, it is the Examiners position that Glennie et al have produced a $F(ab)_2$ that is free of contaminating arsenite. Further, because an antibody molecule consists of two identical light chains and two identical heavy chains, the $F(ab)_2$ taught by Glennie et al, inherently is homogenous as to the heavy chain C-terminal amino acid residue. Glennie et al do not specifically teach a monospecific $F(ab)_2$ or a homogenous heavy chain C-terminal amino acid sequence of Cys-Ala-Ala. These deficiencies are made up for in the teachings of Wahl et al and Cunningham et al.

Wahl et al teach monoclonal anti-carcinoembryonic antigen (CEA) $F(ab)_2$ fragments (i.e., monospecific $F(ab)_2$) are superior for radioimmunodetection and localization of tumors compared to intact antibody or Fab fragments (see entire document, particularly page 324). Wahl et al teach that monoclonal $F(ab)_2$ fragments give better and more rapid specific tumor localization than intact antibody or Fab fragments and $F(ab)_2$ fragments offer significant promise for tumor imaging and possibly therapy (see abstract).

Cunningham et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a monospecific $F(ab)_2$ wherein each F(ab) of the $F(ab)_2$ has only one hinge region cysteine and does not contain hinge region intrachain disulfide bonds, is free of contaminating arsenite and is homogenous as to the heavy chain C-terminus, having the amino acid sequence Cys-Ala-Ala for therapeutic benefit of tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a monospecific $F(ab)_2$ wherein each F(ab) of the $F(ab)_2$ has only one hinge region cysteine and does not contain hinge region intrachain disulfide bonds, is free of contaminating arsenite and is homogenous as to the heavy chain C-terminus, having the amino acid sequence Cys-Ala-Ala for therapeutic benefit of tumors in view of Glennie et al and Wahl et al and Cunningham et al because Glennie et al teach a bispecific $F(ab)_2$ containing thioether-linked Fab fragments and coupling can occur through a single hinge region cysteinyl sulfur and

$F(ab)_2$ having more than one cysteine in the hinge region results in heterogeneity in $F(ab)_2$ preparations such as intra-hinge disulfide formation and contamination with intact parent antibody as well as a minor species of $F(ab)_3$ and Wahl et al teach monoclonal anti-CEA $F(ab)_2$ fragments (i.e., monospecific $F(ab)_2$) are superior for radioimmunodetection and localization of tumors compared to intact antibody or Fab fragments and $F(ab)_2$ fragments offer significant promise for tumor imaging and possibly therapy. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a monospecific $F(ab)_2$ wherein each F(ab) of the $F(ab)_2$ has only one hinge region cysteine and does not contain hinge region intrachain disulfide bonds, is free of contaminating arsenite and is homogenous as to the heavy chain C-terminus, having the amino acid sequence Cys-Ala-Ala for therapeutic benefit of tumors in view of Glennie et al and Wahl et al and Cunningham et al because Cunningham et al teach that alanine substitutions eliminate the side chain beyond the β carbon, yet do not alter the main-chain conformation (as can glycine or proline) nor does it impose extreme electrostatic or steric effects. Therefore, it would have been obvious to the skilled artisan at the time the invention was made to have produced a monospecific $F(ab)_2$ for radioimmunodetection and localization of tumors as taught by Wahl et al and to have used a single hinge cysteine to abolish some sources of heterogeneity in the monospecific $F(ab)_2$ preparations as taught by Glennie et al and to have produced a monospecific $F(ab)_2$ wherein each Fab heavy chain comprises the C-terminal sequence of Cys-Ala-Ala because the single cysteine in the sequence Cys-Ala-Ala allows the directed formation of a more

homogenous preparation of inter-Fab non-disulfide bonds and the two alanines provide stability and protection to the non-disulfide interchain bridge without affecting the main chain conformation or imposing electrostatic or steric effects, which would destabilize or alter the function of the monospecific $F(ab)_2$. Thus, it would have been obvious to one skilled in the art to have produced a monospecific $F(ab)_2$ wherein each F(ab) of the $F(ab)_2$ has only one hinge region cysteine and does not contain hinge region intrachain disulfide bonds, is free of contaminating arsenite and is homogenous as to the heavy chain C-terminus, having the amino acid sequence Cys-Ala-Ala for therapeutic benefit of tumors in view of Glennie et al and Wahl et al and Cunningham et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

15. No claim is allowed.

16. Applicant's request for an interview with the Examiner and his Supervisor is acknowledged, however, because of time constraints Applicant is invited to contact the Examiner at the number below for an interview.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827